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When the metabolism meets the cell cycle in bacteria

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Abstract:	Nutrients availability is the sinews of the war for single microbial cells, driving growth and cell cycle progression. Therefore, coordinating cellular processes with nutrients availability is crucial, not only to survive upon famine or fluctuating conditions but also to rapidly thrive and colonize plentiful environments. While metabolism is traditionally seen as a set of chemical reactions taking place in cells to extract energy and produce building blocks from available nutrients, numerous connections between metabolic pathways and cell cycle phases have been documented. The few regulatory systems described at the molecular levels show that regulation is mediated either by a second messenger molecule or by a metabolite and/or a metabolic enzyme. In the latter case, a secondary moonlighting regulatory function evolved independently of the primary catalytic function of the enzyme. In this review, we summarize our current understanding of the complex cross-talks between metabolism and cell cycle in bacteria.
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When the metabolism meets the cell cycle in bacteria

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23 **Highlights**

24 • Metabolism and cell cycle are interconnected at multiple levels in bacteria

25

26 • DNA replication and cytokinesis are processes subject to metabolic regulation

27

28 • DNA replication initiation rate and cell size can increase at high growth rate

29

30 • Metabolic enzymes bound to their substrates can interfere with activity of the

31 replisome and the divisome

32

33

Summary

Nutrients availability is the sinews of the war for single microbial cells, driving growth and cell cycle progression. Therefore, coordinating cellular processes with nutrients availability is crucial, not only to survive upon famine or fluctuating conditions but also to rapidly thrive and colonize plentiful environments. While metabolism is traditionally seen as a set of chemical reactions taking place in cells to extract energy and produce building blocks from available nutrients, numerous connections between metabolic pathways and cell cycle phases have been documented. The few regulatory systems described at the molecular levels show that regulation is mediated either by a second messenger molecule or by a metabolite and/or a metabolic enzyme. In the latter case, a secondary moonlighting regulatory function evolved independently of the primary catalytic function of the enzyme. In this review, we summarize our current understanding of the complex cross-talks between metabolism and cell cycle in bacteria.

Introduction

Fluctuation in nutrients availability is likely the most common stress faced by single-cell microorganisms in their natural environments. Hence, both eukaryotic and prokaryotic cells use mechanisms to sense nutrient availability and accordingly regulate key steps in cell cycle progression [1,2]. DNA replication is an essential energy consuming process and it is therefore crucial for all living cells to proceed to DNA replication in optimal conditions. Likewise, cell division should take place only when chances of survival are high for daughter cells. In this review, we highlight the extensive cross-talks between metabolism and cell cycle described in bacterial model organisms. We also discuss the importance of cell cycle regulation by metabolism not only in the context of checkpoints when nutrients become scarce, but also in the case of steady state regulation that ensures cell size adaptation and homeostasis during balanced growth.

Metabolic control of DNA replication and segregation

An ounce of prevention is worth a pound of cure

In addition to being highly energy-demanding, DNA replication exposes ongoing replication forks to mutagenic damage by reactive species, including those generated by metabolic activities. It is therefore not surprising that cells use checkpoint mechanisms to monitor the metabolic status before starting chromosome replication and thereby minimize the risk of interrupting replication once started. A well-known metabolic regulator of DNA replication initiation is the hyperphosphorylated nucleotide guanosine penta- and tetra-phosphate, commonly referred to as (p)ppGpp, whose levels increase in response to nutrient starvation [3-6]. The role of (p)ppGpp has been

particularly well studied in the γ -proteobacterium *Escherichia coli* and the α -proteobacterium *Caulobacter crescentus*. In *E. coli*, this molecule binds RNA polymerase (RNAP) [7,8], reducing the transcription of many genes such as *dnaA* coding for the DNA replication initiator protein [9] (**Figure 1**). Overexpression of *dnaA* *in trans* using a (p)ppGpp-insensitive promoter restores initiation of DNA replication in cells accumulating (p)ppGpp, suggesting that the neo-synthesis of active DnaA-ATP molecules is the limiting factor for initiating DNA replication under nutrient limitation [10,11]. However, the number of initiation events upon *dnaA* overexpression remains lower in cells that produce high (p)ppGpp levels than in unstressed cells harbouring basal low levels of (p)ppGpp. Interestingly, this discrepancy is suppressed in cells expressing a mutant RNAP that is blind to (p)ppGpp, suggesting that other transcripts whose levels are modulated by (p)ppGpp are involved in the DNA replication control [10]. Several other genes whose expression is reduced when (p)ppGpp accumulates might be involved, including *gidA* (tRNA modifying enzyme) located just next to *oriC*, *gyrA* and *gyrB* (DNA gyrase), *parC* and *parE* (Topoisomerase IV). The DNA gyrase (*gyrAB*) and the topoisomerase IV (*parCE*) act *in trans* to relax positive supercoils at *oriC*, thereby promoting DNA replication initiation. On the other hand, transcription initiation from *gidA* promoter, reading away from *oriC*, works *in cis* by introducing negative supercoils towards *oriC*, which also promotes initiation of DNA replication. (**Figure 1**) [12]. Interestingly, the expression of an inhibitor of DNA gyrase (*sbmC*) is, on the contrary, inhibited by (p)ppGpp [13], further supporting a negative control of *oriC* superhelicity by (p)ppGpp.

Even in the absence of nutrient deprivation, (p)ppGpp plays a critical role in coordinating growth with cell cycle progression [14,15]. Indeed, as a fast-growing

97 bacterium, *E. coli* adapts the rate of DNA replication initiation to growth rate by
98 increasing the number of replicating chromosomes per cell cycle in nutrient-rich
99 conditions. Hence, the *ori:ter* ratio – that represents the average number of DNA
100 replication initiation events – is inversely proportional to the doubling time. But this
101 correlation is abolished in cells unable to synthesize (p)ppGpp where multiple DNA
102 replication forks occur even at slow growth rates [14]. Here again, this effect may arise
103 from a transcriptional control given that RNAP mutations that mimic the effects of
104 (p)ppGpp binding reinstate low *ori:ter* ratios at slow growth rate in the absence of
105 (p)ppGpp [14].

106 In *C. crescentus*, (p)ppGpp delays the G1-S transition and modulates the levels of
107 DnaA and CtrA. CtrA is a response regulator activated by phosphorylation that
108 regulates transcription of cell cycle genes and represses DNA replication initiation by
109 binding the single *Caulobacter* origin of replication (*Cori*) [16]. Upon carbon or nitrogen
110 starvation, DnaA levels decrease while elevated levels of active CtrA~P are maintained
111 [17-22]. There is evidence that the decrease in DnaA levels involves both
112 transcriptional and (post-)translational regulation. First, transcription of *dnaA*
113 decreases when (p)ppGpp is bound to RNAP (Coppine & Hallez, unpublished).
114 Second, translation of *dnaA* is inhibited upon nutrient starvation and this inhibition
115 relies on a 5' untranslated region (5' UTR) but seems to be (p)ppGpp-independent [22].
116 Finally, DnaA is degraded by at least two ATP-dependent proteases – Lon and ClpAP
117 – and these proteolytic events require (p)ppGpp to some extent [20,21,23,24]. Since
118 the nature of the nucleotide bound to DnaA influences its stability – with DnaA-ATP
119 being somewhat more stable than DnaA-ADP [25]– it is tempting to speculate that one
120 of the proteases might preferentially degrade one of the DnaA forms. In support of that,

Lon was recently shown to poorly degrade the hyperactive ATP-bound DnaA_{R357A} mutant, suggesting that ClpAP might be required to clear active DnaA-ATP from starved cells, such as those entering into stationary phase [24]. In *E. coli*, a different phosphate-based metabolite, polyphosphate (PolyP), stimulates Lon-dependent proteolysis of DnaA-ADP. Since DnaA-ATP is constantly converted to DnaA-ADP, PolyP-Lon regulatory process leads to an inhibition of DNA replication initiation (**Figure 1**) [26]. Although PolyP also modulates cell cycle progression in *C. crescentus*, it remains to be determined if this effect involves proteolytic events [27].

Many studies highlighted a tight link between the initiation step of chromosomal replication and global metabolic pathways such as the central carbon metabolism (CCM). For instance, the temperature-sensitivity of *E. coli* mutants defective in DNA replication initiation (*dnaA46* allele) is suppressed upon inactivation of genes involved in the acetate overflow pathway (**Figure 2**) [28]. These suppressor strains accumulate higher intracellular levels of acetate and addition of exogenous acetate to the growth medium is sufficient on itself to restore growth of *dnaA46* cells at high temperature [29]. Interestingly, DnaA can be acetylated on a conserved Lysine residue in a growth-dependent pattern by the major acetyltransferase of *E. coli* (YfiQ), which uses Acetyl-CoA as a substrate, and this acetylation reduces DnaA activity [30]. Since inactivating *yfiQ* also suppresses *dnaA46* thermosensitivity [29], mutations in the acetate overflow pathway could decrease Acetyl-CoA levels, which in turn might reduce DnaA46 acetylation, thereby triggering its activity. Interestingly, intracellular levels of Acetyl-CoA was shown in the yeast *Saccharomyces cerevisiae* to promote entry into the cell cycle by inducing acetylation of histones [31].

As a fast-growing bacterium, *B. subtilis* also adapts rate of DNA replication initiation to nutrient availability. Interestingly, inactivating the terminal part of glycolysis (e.g. *gapA*) (**Figure 2**) prevents cells from increasing their *ori:ter* ratio under fast-growing regimen [32]. Strikingly, several other metabolic pathways (e.g. fatty acid synthesis, respiration, ...) behave similarly, since their inactivation leads to a low *ori:ter* ratio even at high growth rates. Although the exact regulatory mechanism still needs to be uncovered, it requires an active DnaA protein and/or an intact *oriC*. Indeed, cells initiating DNA replication in an *oriC*- and/or DnaA-independent way are insensitive to growth rate [32]. Finally, a citrate synthase (CitA) has been recently discovered in *C. crescentus* to trigger the G1-S transition by down-regulating CtrA~P activity [33]. In *C. crescentus*, the overall citrate synthase activity is catalysed by two paralogous enzymes (CitA and CitB) but only CitA regulates cell cycle progression. Although the enzymatic activity of CitA is dispensable for mediating cell cycle control, CitA presumably still monitors substrate availability. Indeed, the catalytically inactive mutants used in this study, CitA^{H303W} and CitA^{H303A} [33], still likely bind Acetyl-CoA and NADH with an affinity similar to wild type [34]. Thus, the CitA-dependent control of CtrA~P might require Acetyl-CoA and/or NADH binding rather than citrate synthase activity.

Better late than never

The elongation step of DNA replication is also subject to metabolic regulations. For example, in several bacterial model organisms such as *B. subtilis*, *E. coli* and *Staphylococcus aureus*, (p)ppGpp binds to the DNA primase DnaG (**Figure 1**), but this binding only leads to a replication arrest in *B. subtilis* [35-38]. Moreover, the loss-of-function mutations in the acetate overflow pathway (**Figure 2**) of *E. coli* described

above also suppress, although incompletely, the thermosensitivity of DNA replication elongation mutants (e.g. *dnaG*(Ts), *dnaN*(Ts)). In *B. subtilis*, loss-of-function mutations in genes involved in the terminal part of glycolysis – where redox reactions take place (**Figure 2**) – suppress the thermosensitivity of *dnaE*(Ts) alleles encoding the lagging strand DNA polymerase [39,40]. The same metabolic mutations suppress lethality of various thermosensitive DNA replication mutants such as *dnaG*(Ts) or *dnaC*(Ts) whereas mutations in genes involved in any other part of CCM – first preparatory part of glycolysis, Pentose Phosphate Pathway (PPP) and the Citric Acid Cycle (CAC) (**Figure 2**) – have no effect [39,40].

Despite the multiple genetic interactions identified between DNA replication and CCM, the molecular mechanisms behind these regulations are still poorly understood. Recently, pyruvate kinase (PykA, **Figure 2**) of *B. subtilis* has been shown to stimulate the DNA polymerase activity of DnaE *in vitro*, likely through a direct protein-protein interaction, however it also inhibits the helicase activity of DnaC [41]. PykA is responsible for the final step of glycolysis by catalysing the transfer of a phosphoryl group from PEP to ADP, generating pyruvate and ATP. Notwithstanding these counterintuitive effects seen *in vitro*, PykA may, as a moonlighting enzyme, directly determine the speed of the replication fork depending on substrate (PEP) availability by modulating replisome activities (**Figure 1**).

Similarly to what happens in yeast [42], the relative abundance of metabolites fluctuates as a function of cell cycle in *C. crescentus* [43]. A corollary is that the redox state oscillates throughout the cell cycle as well. Indeed, new-born cells in G1 phase have a more reduced cytoplasm, which becomes oxidized during S phase, and then

returns to a more reduced state at the end of chromosome replication and the onset of cytokinesis [44]. The oxidized environment during DNA replication (S phase) promotes the activation of NstA, an inhibitor of topoisomerase IV (ParCE), through the formation of intermolecular disulfide bonds between NstA monomers [44] (**Figure 1**). Thus, the oscillation of the redox state throughout the *Caulobacter* cell cycle restricts the decatenation activity of the topoisomerase IV to late predivisional cells, and inhibits this activity during active replication.

Metabolic control of cytokinesis

The more you eat, the bigger you are

Fast-growing bacteria such as *E. coli*, *B. subtilis*, *Salmonella typhimurium* or *Pseudomonas aeruginosa* adapt their cell size according to nutrient availability [2,45-47]. For example, *E. coli* cells grown in rich medium are twice as long as cells cultivated in nutrient-poor conditions (**Figure 3A**). Both *B. subtilis* and *E. coli* coordinate growth rate with cell division by monitoring UDP-glucose levels thanks to non-orthologous glucosyltransferases, respectively UgtP and OpgH [48,49]. The binding of their substrate – UDP-glucose which accumulates in cells under nutrient-rich conditions – stimulates direct interaction with FtsZ, a highly conserved tubulin-like protein that assembles at the division site as a scaffolding structure called the Z-ring [48,50]. The cytoplasmic protein, UgtP, prevents Z-ring assembly in a concentration-dependent manner and the membrane-associated protein, OpgH, acts as a non-competitive inhibitor, sequestering FtsZ. Both proteins effectively raise the apparent critical concentration for FtsZ assembly and GTP hydrolysis in the presence of elevated UDP-glucose [48] (**Figure 3B**). In addition to activation by substrate binding, UgtP levels are

regulated by Clp-dependent proteolysis with *clpC* and *clpE* expression being induced under nutrient-poor conditions [51]. It is noteworthy that although *E. coli* and *B. subtilis* cells lacking *opgH* or *ugtP*, respectively, are smaller than wild-type cells, they still present a narrow Gaussian cell size distribution, suggesting that the metabolic control of cell size is superimposed on the mechanism responsible for cell size homeostasis.

Pyruvate or fatty acids on the menu to keep one's figure

Pyruvate is another important metabolite that modulates cell division in *B. subtilis* [52] (**Figure 2**). Indeed, *pykA* mutations that prevent synthesis of pyruvate from PEP, suppress the thermosensitivity of the *ftsZ(ts1)* allele and lead to cell division defects in an otherwise wild-type background, with cells harbouring several Z-rings as well as minicells [52]. More strikingly, addition of exogenous pyruvate to the growth medium not only restores the thermosensitivity of *ftsZ(ts1)* in a *pykA* mutant background but also suppresses cell division defects of *pykA* mutant cells. Although evidence suggests a role of the E1 α subunit of the pyruvate dehydrogenase (PDH-E1 α), the mechanism and the proxy by which pyruvate levels control FtsZ dynamics remain unknown.

Fatty acid biosynthesis (**Figure 2**) is another metabolic pathway described to regulate cell size in different microorganisms. Indeed, the inactivation of early steps of fatty acid biosynthesis ($\Delta fabH$) in *E. coli* decreases the rate of inner membrane lipid biogenesis, which leads to a ~70% reduction of cellular volume, [53]. Strikingly, this effect seems to be specific to fatty acid biosynthesis since inhibiting the synthesis any other membrane constituents either reduces cell size in a lipid-dependent way or does not impact cell size [54]. For a long time, nutrient availability has been proposed to be coupled to the rate of fatty acid biosynthesis in *E. coli* [55,56], but again the underlying

mechanism and the exact role played by FabH in this process remain to be determined. The proximity between PykA, PDH and FabH on the metabolic map (**Figure 2**) raises the interesting hypothesis of a possible link between the observed cell division defects of all these mutants and the initial step of fatty acids metabolism. In support of that, fatty acids were recently shown to be a key molecular determinant of cell size control in fast-growing prokaryotic and eukaryotic microorganisms [54].

pHine tuning cytokinesis, the acid test

External stimuli such as pH variation can also control cell size as reported in *E. coli*, *S. aureus*, *Streptococcus pneumoniae* and *C. crescentus* [57-59]. For instance, compared to growth in neutral pH, *E. coli* cells grown under acidic conditions have 25% less volume, and cells grown in alkaline conditions have 20% more volume (**Figure 3A**). Growth in acidic media stimulates cytokinesis by favouring the recruitment of the late cell division protein FtsN to the division machinery, which triggers constriction and septal wall synthesis. Therefore, cells grown in acidic conditions are shorter than their counterparts grown in alkaline conditions. Similarly, in *Salmonella*, external pH modulates the activity of two peptidoglycan (PG) synthase paralogs, PBP3 and PBP3sal. These PG transpeptidases actively participate in septum synthesis and promote cell division in the acidic environment of the phagosome during infection [60]. In *C. crescentus*, glutathione levels oscillate throughout the cell cycle and indirectly influence cytokinesis [43]. Mutants unable to synthesize glutathione display defects in cytokinesis that were primarily attributed to dysregulation of the potassium efflux K^+/H^+ antiporter, KefB, whose activity is inhibited by glutathione [43]. However, in the absence of glutathione, whether cytokinesis is impacted by a reduction of intracellular

K⁺ or a more acidic pH remains to be determined knowing that both cations affect FtsZ dynamics *in vitro* and cell size *in vivo* [58,61-63].

Dividing when sated

C. crescentus uses GdhZ (a NAD-dependent glutamate dehydrogenase) and KidO (a NAD(H)-binding protein) to coordinate cytokinesis with metabolism by monitoring glutamate and NADH cellular supplies [64,65]. When bound to substrate, glutamate or NAD⁺ for GdhZ and NADH for KidO, these proteins act in synergy to negatively regulate the Z-ring structure. KidO prevents lateral interactions between FtsZ protofilaments while GdhZ shrinks protofilaments by stimulating the GTPase activity of FtsZ. As substrate binding is required for GdhZ and KidO to regulate FtsZ dynamics [64,65], localization of both regulators in the vicinity of the Z-ring during constriction might further enhance their concerted action by funnelling the NADH generated by GdhZ to KidO (**Figure 3B**). In addition, GdhZ and KidO activities are restricted to the early and late stages of the cell cycle thanks to the degradation of both regulators by the ClpXP protease. This temporal regulation prevents premature assembly of the cell division machinery in new-born cells and stimulates the disassembly of the Z-ring at the end of the cell cycle [64,65]. Like pyruvate, glutamate is also a central cellular metabolite, located at the edge of the nitrogen cycle and the CAC (**Figure 2**). By coordinating cytokinesis with metabolic activity (i.e. nutrient availability), cells ensure completion of cytokinesis and release of progeny when growth conditions are optimal. Interestingly, the cell division control mediated by GdhZ seems conserved among α -proteobacteria, at least in the facultative intracellular pathogen *Brucella abortus* [66].

Concluding remarks

The number of genetic interactions between DNA replication or cytokinesis and metabolic mutants strongly suggests that these essential processes are interconnected, with some metabolic reactions linked to multiple steps of the cell cycle. The inactivation of the highly conserved pyruvate kinase encoding gene *pykA* can fully suppress the lethality of DNA replication elongation mutants (e.g. *dnaE(Ts)*) in *E. coli* [52] as well as the thermosensitivity displayed by *B. subtilis ftsZ(ts1)* cells [52]. Whether the pyruvate kinase regulates both cell cycle stages in the same species remains to be tested but the central position of pyruvate for several metabolic pathways (neoglucogenesis, amino acids synthesis, CAC, fatty acids synthesis) makes this metabolite a perfect candidate to monitor nutrient availability (**Figure 2**). But what are the underlying mechanisms? How does metabolism influence cell cycle progression? One can speculate that a metabolite whose concentration rapidly changes upon stress, alone or bound to an enzyme as a substrate or a ligand, directly interacts with a component of the replisome to regulate its activity. In support of that, metabolic enzymes were found in high-throughput protein-protein interactions screens as physical partners of replisome components both in *E. coli* and *B. subtilis* [67,68]. Additionally, the viability of thermosensitive DNA replication mutants was greatly improved when the growth medium was supplemented with CCM metabolites [69]. Alternatively, the metabolite whose concentration changes upon stress might be used as a substrate for enzymes that mediate post-translational modifications (acetylation, phosphorylation, ...) of a replisome component, such as the acetylation of DnaA [30]. The composition of the cytoplasmic membrane is another non-exclusive proxy used to transduce the metabolic status to the replisome, at least for the initiation step since

312 acidic phospholipids have been shown to stimulate DnaA activation by regenerating
313 DnaA-ATP [70,71].

314 Whatever the mechanism transducing the signal from metabolism to influence the cell
315 cycle is, it relies on metabolites whose intracellular concentrations fluctuate upon
316 environmental changes and thereby report environmental status (e.g. UDP-Glucose
317 for the central carbon metabolism or glutamine for nitrogen metabolism). For instance,
318 *Caulobacter* and *Sinorhizobium meliloti* cells monitor intracellular glutamine levels as
319 a proxy for nitrogen availability with the help of the nitrogen-related
320 phosphotransferase system (PTS^{Ntr}), which leads to (p)ppGpp accumulation upon
321 glutamine deprivation [72-74]. Rather than only gears providing energy and building
322 blocks, increasing evidence supports metabolism as overseeing major cellular
323 processes such as DNA replication and cytokinesis. Now we need to understand how
324 these regulatory phenomena work at the molecular level.

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Conflict of interest

The authors declare that they have no conflict of interest.

Figure legends

Figure 1 Overview of the initiation (1) and elongation (2) steps of DNA replication in bacteria

(1) The initiator protein DnaA bound to ATP (DNA^{ATP}, red) binds the single origin of replication (*oriC*) to separate DNA strands and helps, together with single-strand binding proteins (dark grey), in recruiting the helicase (DnaB, green) in complex with the helicase loader (DnaC, pink). (2) The DNA primase (DnaG, purple) is recruited to initiate transcription of short RNA primers (red lines), DNA^{ATP} is converted to DNA^{ADP} and DnaC is released from the initiation complex. The multisubunit DNA polymerase III (dark blue) together the sliding clamp (DnaN, yellow) starts to synthesize DNA continuously from the leading strand (brown line) and discontinuously from the lagging strand (blue line). The topoisomerase IV and the DNA gyrase concomitantly introduce negative supercoiling upstream of the DNA polymerase III. The regulation mediated by (p)ppGpp, PolyP, Lon, ClpAP, PykA and NstA, described in the text, are represented in light grey with dashed lines.

Figure 2 Schematic overview of the metabolic routes involved in the metabolic control of cell cycle in bacteria

Regulatory enzymes are indicated in red, while metabolites used as a proxy for cell cycle control are represented in light blue. The cell cycle components targeted by the metabolic enzymes are indicated in green. OPG, Osmoregulated periplasmic glucans; F 6-P, Fructose 6-phosphate; F 1,6-BP, Fructose 1,6-biphosphate; DHAP, Dihydroxyacetone-P; GAP, Glyceraldehyde-3-P; 1,3 BPG, 1,3-Bisphosphoglycerate; 3-PG, 3-P-Glycerate; 2-PG, 2-P-Glycerate; PEP, Phosphoenolpyruvate; α -KG, alpha-ketoglutarate. Pyk, Pyruvate kinase; PDH, Pyruvate dehydrogenase; Cit, Citrate synthase; FA, Fatty acids.

Figure 3 Molecular mechanisms used by bacteria to coordinate metabolism with cell division

(A) The size of fast-growing bacteria grown in rich conditions (e.g. high intracellular concentration of UDP-Glucose) or at alkaline pH can be twice longer than the ones grown in poor conditions or at acidic pH. The Z-ring is represented in green, FtsN in

615 grey and metabolites used as a proxy for this regulation (e.g. UDP-Glucose) are
616 represented in light blue. The replicating DNA molecules are represented in black. (B)
617 Proteins coordinating metabolism with cell division interfere with Z-ring dynamics by
618 using different molecular mechanisms. UgtP in *B. subtilis* and OpgH in *E. coli* interfere
619 with the Z-ring dynamics by respectively severing or sequestering FtsZ molecules
620 (green) only when the UDP-Glucose (light blue hexagon) is highly concentrated. GdhZ
621 bound to its substrate (glutamate, light blue square) or its cofactor (NAD⁺, light orange
622 star) shrinks FtsZ protofilaments by stimulating its GTPase activity while KidO bound
623 to NADH (light blue star) interferes with the lateral interactions between FtsZ
624 protofilaments.

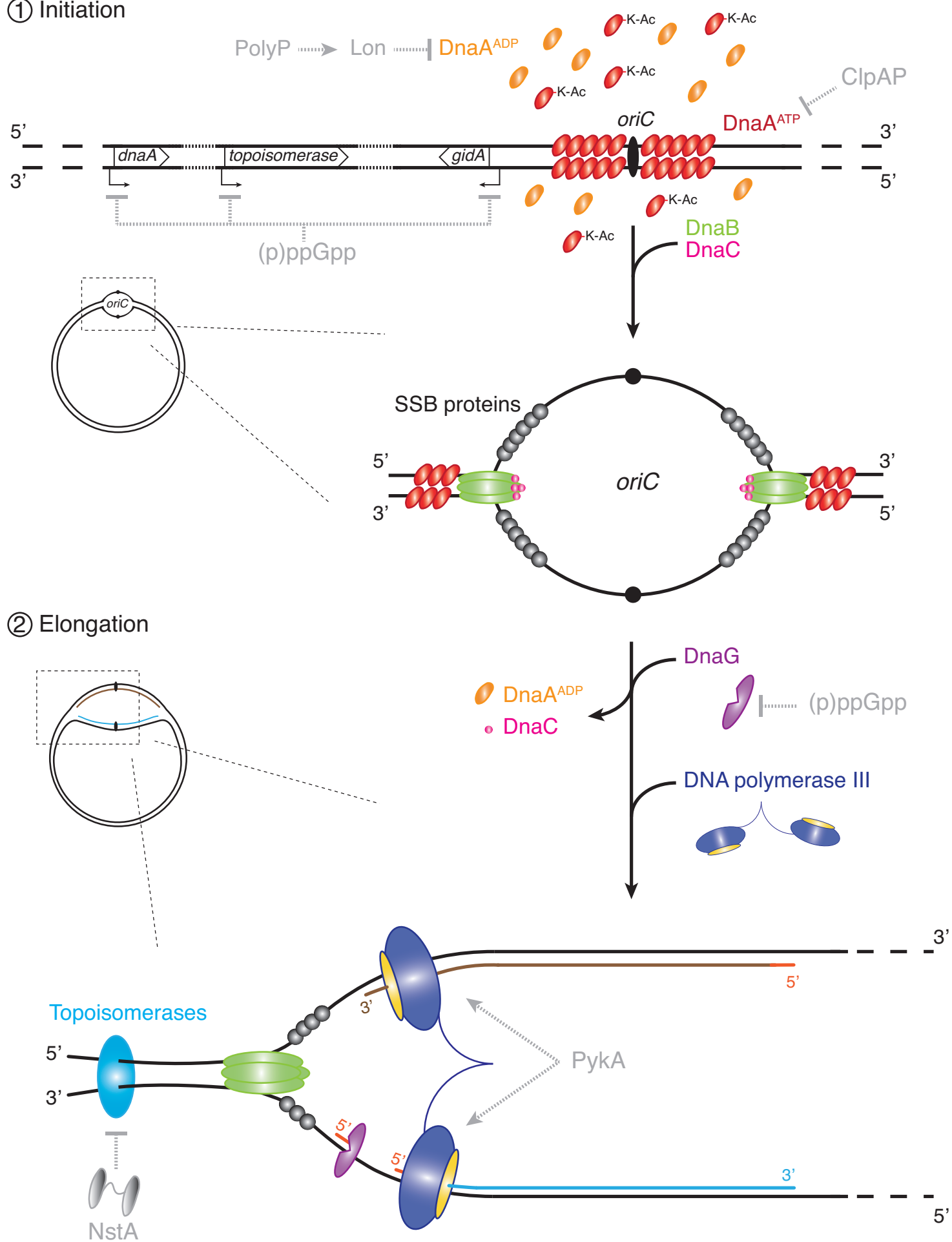
Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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② Elongation



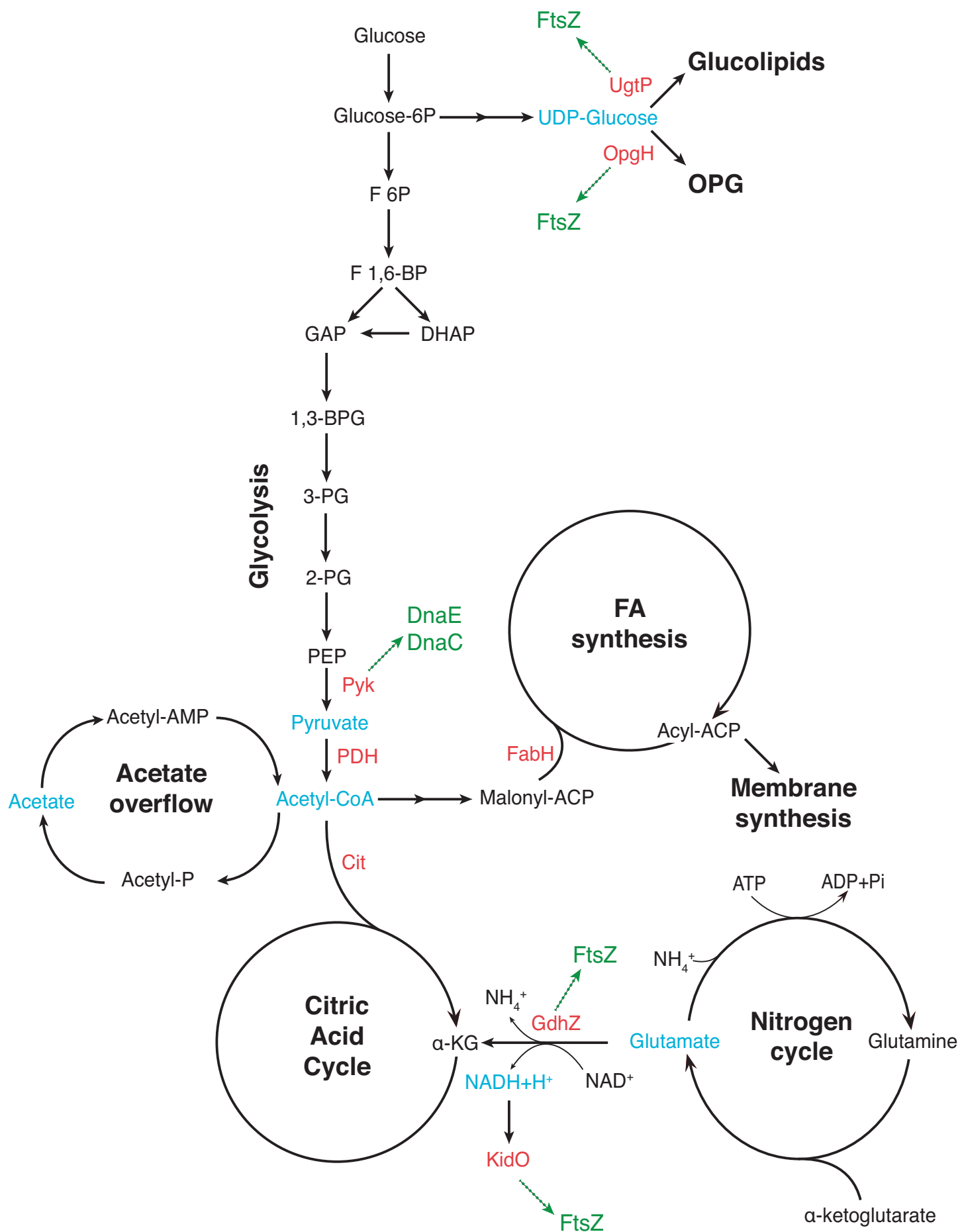
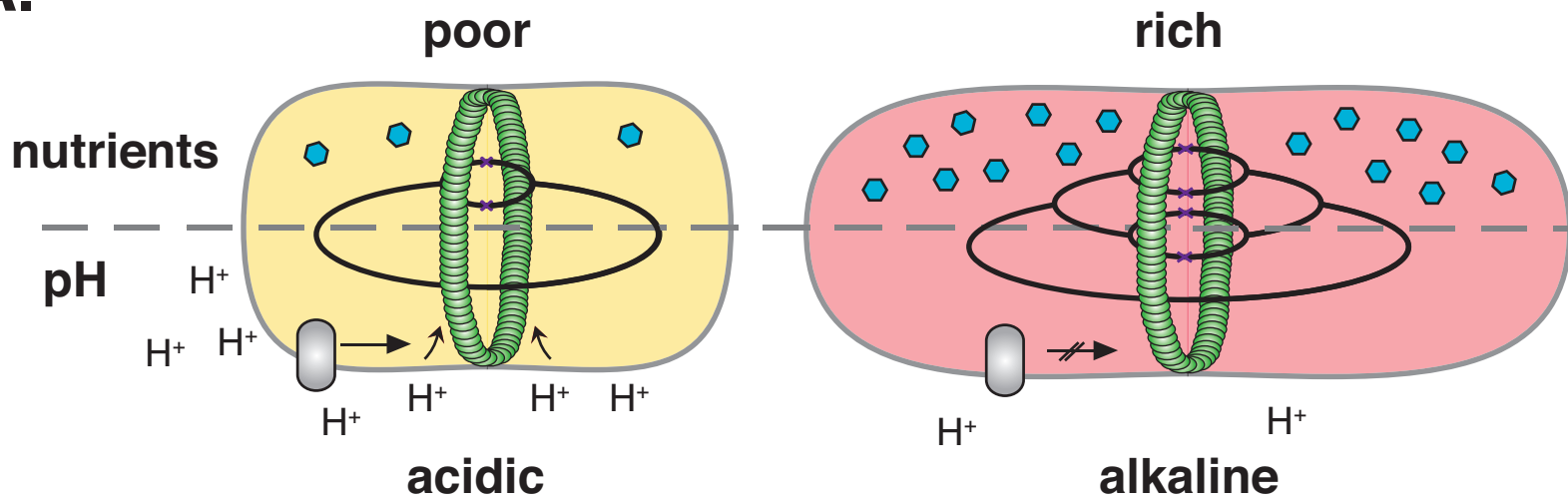


Figure 3

A.



B.

